REMARKS

Applicant's counsel thanks the Examiner for the careful consideration given the application. The present application contains claims 11-21. Claim 11 has been herein amended.

35 USC § 112

Claim 11 has been amended by deleting the phrase "generally associated with pain and fever" to meet the Examiner's objection of indefiniteness in paragraph 7 of the Office action. The word "drastically" has been deleted to overcome the objection of clarity and indefiniteness in paragraph 8. It has been specified that the term "therapeutic effect" refers to the therapeutic effect of treatment of inflammatory symptoms, as requested by the Examiner in paragraph 6.

35 USC § 102 and 103

Novelty

Claims 11 -13 have been rejected under Section 102(b) as being anticipated by Kerouac et al. (WO 99/40898).

Claims 11 - 13 and 21 have been rejected under Section 103(a) as being unpatentable over Kerouac et al. (WO 99/40898) in view of Mehta et al. (WO 01/85134).

WO 01/85134 (Mehta S. et al.) describes a pharmaceutical composition for buccal administration of a pharmaceutical active ingredient, such as a non-steroidal analgesic or an anti-inflammatory drug, having very fast disintegrating properties in the buccal cavity. Examples of active ingredients are nimesulide and piroxicam.

WO 01/85134 does not disclose a method of administering a sublingual pharmaceutical formulation for the treatment of inflammatory symptoms of various types comprising an anti-inflammatory agent in reduced dose with respect to the dose of the same active ingredient in a pharmaceutical composition for oral administration.

It is well known in the field that the buccal administration pathway is different from the sublingual administration pathway. Sublingual administration means "administration of a soluble dosage

form by placement under the tongue", while buccal administration means "administration of a soluble dosage form between the cheek and gingival; it may involve direct application of a drug onto the buccal mucosa, as by painting or spraying" (see for example the on-line medical dictionary). Since the bottom of the tongue has a different blood supply with respect to the upper part of the tongue and the buccal cavity, the bioavailability, the absorption speed, the therapeutic effect that can be achieved and the dosage required are different.

The subject-matter of claim 11 is therefore novel over Mehta S. et al.

WO 99/40898 (Kerouac R. et al.) describes a sublingual formulation comprising, among other components, an anti-inflammatory agent, such as flurbiprofen, diclophenac, indomethacin, ketoprofen, tenoxicam, in dosage equal to or near standard oral dosages. WO 99/40898 does not disclose that the therapeutic dose of said anti-inflammatory agent in said sublingual formulation is reduced in comparison with the therapeutic dose of the same anti-inflammatory agent in a pharmaceutical formulation for oral administration.

Therefore, the subject-matter of claim 11 is novel over Kerouac R. et al.

Inventive step/Non-obviousness

WO 99/40898 describes a sublingual formulation containing a dosage of active principle that is equal to the dosage of active ingredient used in formulations for oral administration. The sublingual composition is administered under the tongue in such a way that a portion of the active principle is absorbed sublingually, giving rise to a first plasmatic peak of the drug, and the remaining portion of the medication is orally absorbed, giving rise to a second plasmatic peak delayed in time from the first plasmatic peak (see page 4, lines 24-29).

According to WO 99/40898, in order to obtain the same therapeutic effect that is achieved with oral administration it is necessary to prepare a sublingual formulation containing the same dosage of active principle as in the oral administration. In this way, a portion of active substance is absorbed under the tongue and gives a quick therapeutic effect and another portion is enterically absorbed, giving a therapeutic effect delayed in time.

The sublingual formulation of WO 99/40898 does not solve the problem underlined by the present invention, that is the provision of a sublingual formulation that can give a quick therapeutic effect and, at the same time, avoid the drawbacks of oral administration, such as gastrointestinal damage, stomach pain and partial elimination through the liver.

The inventor of the present sublingual formulation has unexpectedly found that the combination of the desired therapeutic effect and low side effects can be achieved by reducing the standard oral dosage of active principle. Moreover, the effect is achieved in a quicker manner with respect to an oral administration. The sublingual formulation of the invention is therefore suitable to treat acute inflammatory conditions, which need a quick response and low side effects.

The rapid onset of the therapeutic effect that can be obtained with the present formulation has been demonstrated with certain experiments described in the attached Declaration of Bruno Silvestrini, which experiments are also set forth here as follows. Two sublingual formulations comprising 25 mg and 50 mg of nimesulide, respectively, and an oral tablet comprising 100 mg of nimesulide were administered to the same panel of 6 patients. The blood concentration of nimesulide was tested at fixed times, starting immediately after administration and up to 8 hours after the administration.

The enclosed graph (EXHIBIT A) shows that with the sublingual formulations of the invention the maximum blood concentration (i.e. the maximum effect) is achieved about half an hour after administration and the effect goes to about zero after about two and a half hours. On the contrary, with the oral administration, the maximum therapeutic effect is achieved after about two hours from administration and remains constant for more than 8 hours.

The above experiments demonstrate the rapid onset of the therapeutic effect of nimesulide and demonstrate that the sublingual formulation of the invention solves the problem of providing a drug formulation for the treatment of acute inflammatory diseases, i.e. pathologies that need a rapid onset of the therapeutic effect and low side effects. Based on the prior art, the results of the present invention are surprising and unexpected. The present inventor has unexpectedly and surprisingly found that the combination of the desired therapeutic effect and low side effects can be achieved by reducing the standard oral dosage of active principle. Moreover, the effect is achieved in a quicker manner than oral administration. Accordingly, the sublingual formulation of the invention is suitable to treat acute inflammatory conditions, which need a quick response and low side effects.

This problem cannot be solved by either an oral formulation nor the sublingual formulation of WO 99/40898. In fact, both the oral formulation and the sublingual composition of WO 99/40898 need a higher dosage of active ingredient to achieve the desired therapeutic effect and the active ingredient is, at least partially, orally absorbed. Thus, side effects such as gastrointestinal damage, stomach pain and partial elimination through the liver are not avoided.

WO 01/85134 describes a buccal formulation containing nimesulide. As already stated above, the buccal administration is different with respect to sublingual administration since the absorption pathway and, therefore, the bioavailability is different. The buccal formulation of WO 01/85134 comprises the same amount of active principle as an oral composition.

Hence, a sublingual composition comprising a reduced amount of active principle characterized by rapid onset of action and low side effects is not suggested by WO 01/85134, even when read in combination with WO 99/40898, since WO 01/85134 suggests administering the active principle buccally and with the same quantity as the standard oral composition, and WO 99/40898 suggests a sublingual composition, having the same amount of active ingredient as the standard oral formulation, in which the active substance is partially enterally absorbed (thus causing the standard side effects of the oral administration, i.e. gastrointestinal damage, stomach pain and partial elimination through the liver).

Since none of the cited documents, either alone or combined, suggest the present sublingual composition, the subject-matter of claim 11 is inventive and non-obvious over the cited prior art.

In view of the amendments and the remarks, and having dealt with all the objections raised by the Examiner, reconsideration and allowance of the application is courteously requested.

When the present application was filed, applicant submitted a Form PTO-1449 listing several references for consideration. In the most recent Office action, the Form PTO-1449 was returned, but four of the references (the WO references) were lined through and the other references were not initialed. Applicant had not sent in copies of the WO references since they were sent to the USPTO by the IB. Apparently these references were lost or misplaced. So that the Examiner can consider these four WO references, applicant is enclosing copies herewith; applicant is also enclosing a copy of the Form PTO-1449 listing all the references and asks that the Examiner consider the references

and enclose an initialed copy of the Form PTO-1449, initialing all the references, with the next communication.

If any additional fees are required by this communication, please charge such fees to our Deposit Account No. 16-0820, Order No. BUG5-39170.

Respectfully Submitted,
PEARNE & GORDON LLP

By _____
John P. Murtaugh, Reg. No. 34226

1801 East 9th Street
Suite 1200
Cleveland, Ohio 44114-3108
Phone: (216) 579-1700
Fax: (216) 579-6073

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